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## ANATOMICAL PATHOLOGY

### Placental fetal vascular thrombosis lesions and maternal thrombophilia

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#### Summary

**Aims:** Following intrauterine fetal death (IUFD), the placental fetal vessels undergo regressive changes. These changes are virtually indistinguishable from lesions that are the result of fetal vascular thrombosis (FVT). This study investigated the relation between these lesions and maternal thrombophilia.

**Methods:** Placenta slides of 65 IUFDs with known maternal thrombophilia test results (compound MTHFR C677T and A1298C heterozygosity,  $n=10$ ; MTHFR 677TT homozygosity,  $n=3$ ; protein S deficiency,  $n=0$ ; factor V Leiden mutation,  $n=2$ ; prothrombin gene mutation G20210A,  $n=1$ ; lupus anticoagulant,  $n=2$ ; antiphospholipid syndrome,  $n=1$ ; MTHFR C677T heterozygosity,  $n=5$ ; MTHFR A1298C heterozygosity,  $n=4$ ; and MTHFR 1298CC homozygosity,  $n=2$ ) and of 30 livebirths with positive maternal thrombophilia test results ( $n=5, 2, 0, 9, 2, 0, 2, 7, 2$  and 1, respectively, for those thrombophilias) were microscopically examined for septation, fetal vessel thrombosis, intimal fibrin cushions, avascular villi, haemorrhagic endovasculitis and fibromuscular sclerosis.

**Results:** Thirty of the 65 IUFDs had a positive maternal thrombophilia test; 22 of these 30 had FVT lesions. Thirty two of the 35 IUFDs with a negative maternal thrombophilia test had FVT lesions. Septation, defined as multiple lumens or 'recanalisation' in a placental vessel, was the lesion seen most often in IUFD ( $n=41$ ) whether by itself ( $n=13$ ) or in combination with other FVT lesions. Five of the 30 livebirths had FVT lesions but septation was not seen in any of the placentas from the 30 livebirths. FVT lesions did not have a significant relation with maternal thrombophilia.

**Conclusions:** The finding of fetal vascular thrombosis lesions in stillbirths does not imply thrombophilia as the cause of the fetal death. Factors other than thrombophilia may play a role in the cause of FVT lesions.

**Key words:** Placenta, pregnancy complications, stillbirth, thrombophilia.

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#### INTRODUCTION

Placental fetal vessels undergo regressive changes following intrauterine fetal death (IUFD). Due to cessation of the fetal circulation, there is progressive sclerosis of the blood vessels in the fetal stem villi with narrowing of their lumina (fibromuscular sclerosis) followed by septation and obliteration. There is hypovascularity followed by stromal fibrosis of terminal villi, which later become avascular.<sup>1–4</sup> These changes are virtually indistinguishable from lesions that are the result of

fetal vascular thrombosis, although changes tend to be more generalised post-mortem.<sup>3,5</sup>

Stem villous vascular septation presents a diagnostic difficulty. It has been proposed that the presence of multiple channels of recanalisation within an organising thrombus implies that the thrombus occurred when the fetus was alive and that abnormal coagulation could be a potential aetiological factor for the thrombus formation and IUFD.<sup>6</sup> In pregnancies with adverse fetal outcomes, such as neonatal seizures and growth restriction, septation of fetal vessels can be seen in association with thrombophilia.<sup>6,7</sup> Septation of fetal vessels can be localised and patchy soon after fetal death<sup>8</sup> and thus it becomes unclear whether the cause of the fetal death is due to fetal thrombotic tendency or the septation of fetal vessels is merely a post-mortem regressive change. It is clinically relevant to distinguish between the two as the former warrants thrombophilia testing and presents a potential modifiable treatment option. The aim of this study was to investigate the relation between maternal thrombophilia and placental stem villous vascular septation and other fetal obstructive vascular lesions.

#### MATERIAL AND METHODS

##### Intrauterine fetal death group

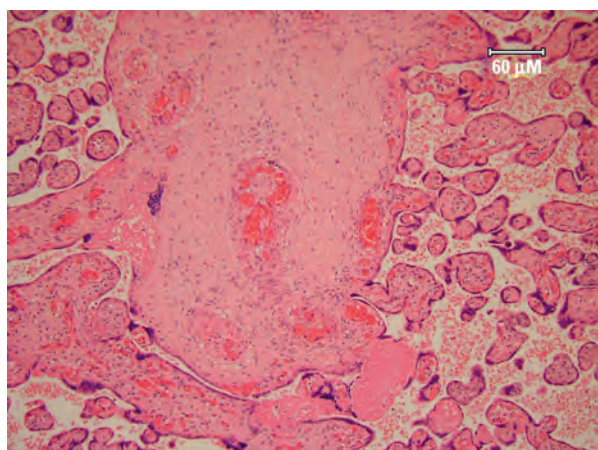
All cases of singleton IUFD of 24 or more weeks gestational age delivered in South Australian public hospitals from January 2001 to December 2006 were studied if the mothers had been tested for thrombophilia according to the recommendations of the Perinatal Mortality Subcommittee of the South Australian Department of Health; autopsies and placental examination of these stillbirths were performed in the Women's and Children's Hospital, North Adelaide.

Thrombophilia test results of the mother were subdivided into clinically significant thrombophilia (MT+) (protein S deficiency, factor V Leiden G1691A, prothrombin G20210A gene mutation, lupus anticoagulant, and antiphospholipid syndrome), clinically less significant thrombophilia (MT–) [compound methyltetrahydrofolate reductase (MTHFR) C677T and A1298C heterozygosity, MTHFR 677TT homozygosity, MTHFR C677T or A1298C heterozygosity, and 1298CC homozygosity] or normal (MTN). Clinically significant thrombophilias are more likely to cause occlusive vascular disease than clinically less significant thrombophilias.<sup>9</sup>

Information about gestational age, maternal age, placental weight, fetal birth weight, previous stillbirths, gestational complications (pre-eclampsia, gestational hypertension, placental abruption, gestational diabetes, umbilical cord complications, chorioamnionitis), fetal complications (growth restriction, fetal asphyxia, fetal infection) and maternal history (smoking, obesity and medication use) was collected for each IUFD from the mother's case notes.

##### Livebirth group

Thirty random placentas from livebirths with positive thrombophilia test results were selected from 2004–2006; these women had been tested because of



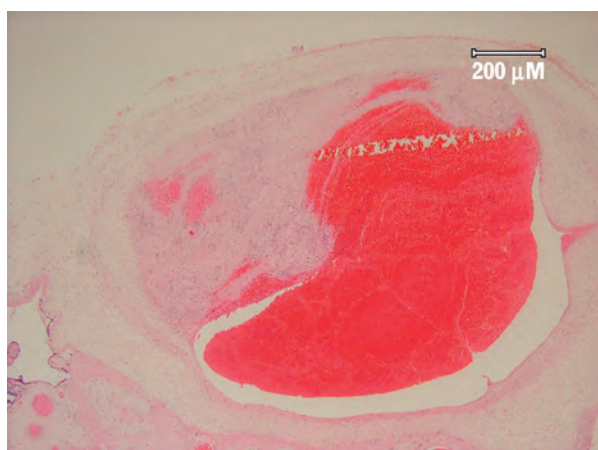
**Fig. 1** Septation of two placental vessels showing multiple lumina which are separated by fibrin deposition containing erythrocytes.

previous adverse obstetric history. Information about maternal age, gestational age, gestational disease, maternal disease and placental weight was collected from the case notes.

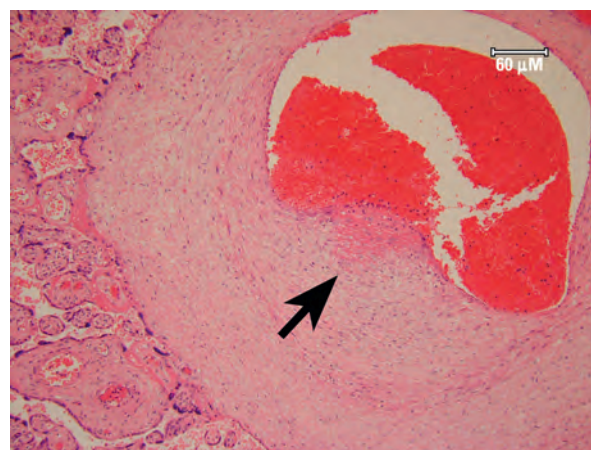
### Histology and definition of lesions

The placental slides of all cases were re-examined without knowledge of the results of the thrombophilia testing. All the placental slides were evaluated for the presence of septation and other putative features of fetal obstructive vascular lesions: fetal vessel thrombus, intimal fibrin cushions, avascular villi, haemorrhagic endovasculitis, and fibromuscular sclerosis.<sup>5</sup> Slides consisted of one enface and one or more parenchymal full thickness sections per case (mean 5 slides, range 2–11 slides).

Septation is defined as the presence of multiple lumina in fetal stem vessels, due to fibroblast ingrowth into the vessels, also called 'recanalisation' or 'partial re-organisation'. There are irregular spaces in the vessels which contain degenerated blood (Fig. 1). A fetal vessel thrombus is defined as the presence of an organised occluding or partly occluding thrombus adhering to the endothelium of the fetal vessel (Fig. 2). Intimal fibrin cushions are seen as fibrin or fibrinoid depositions (subendothelial or intramuscular), which are generally located within the wall of a chorionic or large stem villous artery (Fig. 3). Avascular villi are defined as more than 15 villi in a section showing a total lack of villous vessels and a hyalinised fibrotic stroma (Fig. 4). Haemorrhagic endovasculitis (HEV) is defined by vessel injury, haemorrhage into the villous stroma, endothelial and medial hyperplasia, karyorrhexis, mural extravasation of erythrocytes, fragmentation of erythrocytes, and occasional haemosiderin deposition in the villous stroma (Fig. 5). Fibromuscular sclerosis is defined as marked thickening of the intimal and medial layers of the stem vessels with luminal obliteration (Fig. 6). While the other five lesions were often solitary



**Fig. 2** Adherent thrombus in a placental fetal vessel.



**Fig. 3** Subendothelial intimal fibrin cushion in a placental fetal vessel (arrowed).

or localised lesions, septation could be multiple and, accordingly, an attempt was made to estimate the extent and severity of septation. The extent of septation was defined as focal (scored as 1), intermediate (scored as 2) or diffuse (scored as 3) if there were fewer than 5, 5–10, or more than 10 septated vessels per slide, respectively; severity was graded by averaging the sum of the extent scores of all the slides per case and defined as mild, moderate or severe with scores of 1, 2, or 3, respectively.

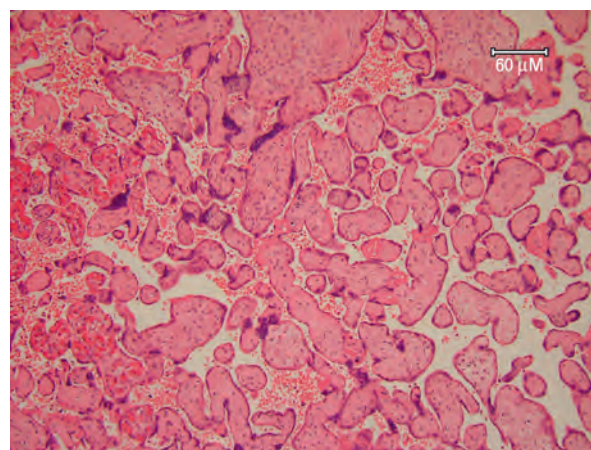
### Statistical analysis

Comparisons between lesions in the fetal vessels and maternal thrombophilia were performed using Fisher's exact test or chi-square test. *p* values calculated by Fisher's test were two-tailed. A *p* value <0.05 was considered statistically significant.

## RESULTS

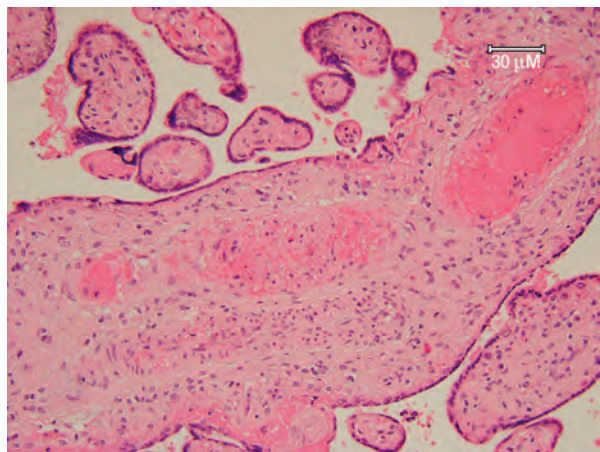
There were 65 IUFDs that fulfilled the study criteria. The mean gestational age of the 65 IUFDs was 33 w (range 24–41 w) and of the 30 livebirths was 38 w (range 36–41 w). The mean maternal age for the IUFD group was 29 y (range 18–43 y) and of the livebirth group 33 y (range 19–46 y).

In the IUFD group, 16 women had experienced a previous IUFD, three women had pre-eclampsia, and 20 delivered a stillbirth with intrauterine growth restriction. Umbilical cord abnormalities were present in seven cases (hypercoiled cord, *n* = 3; true knot, *n* = 1; reduced cord coiling, *n* = 1; excessively long cord, *n* = 2). Placental abruption was diagnosed in two

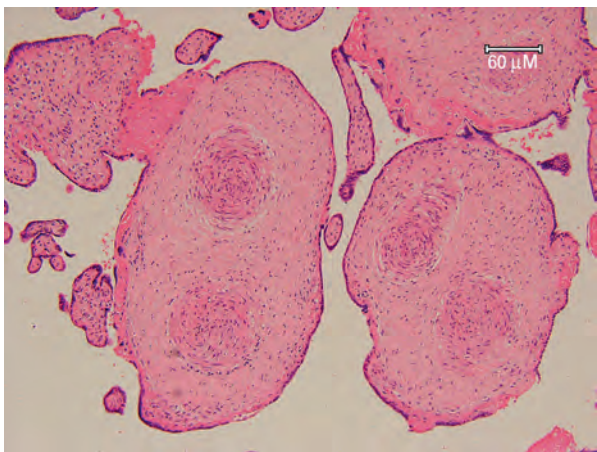


**Fig. 4** Tract of avascular villi with bland hyalinised fibrotic stroma and a lack of capillaries (right) contrasting with vascular villi (left).





**Fig. 5** Haemorrhagic endovasculitis with karyorrhexis, diapedesis of erythrocytes and mural disruption.



**Fig. 6** Fibromuscular sclerosis with thickening of the intimal and medial layers of the vessel wall and complete luminal obstruction.

cases. In the livebirth group, a previous IUFD was reported in 17 cases; one case had pre-eclampsia and three livebirths were growth restricted.

The frequencies of the examined placental lesions and the relationship to thrombophilia test results are shown in Tables 1 and 2 for the IUFDs and livebirths, respectively. In the IUFD group, 11 (16.9%) cases did not have any lesion and of this group, eight cases had a positive maternal thrombophilia test result. In the livebirth group, which had been selected randomly on the basis of a positive maternal thrombophilia test, 25 cases (83.3%) did not have any lesion. Septation was the most frequently seen lesion in the 65 IUFD cases, found as a single lesion in 13 cases (20%) and in combination with other lesions in 28 other

cases but it was not seen in any of the placentas of the 30 livebirths.

Six of the 30 IUFD cases with a positive maternal thrombophilia test result (MT+, MT–) were clinically significant (MT+), of which five had one or more of the examined thrombotic placental lesions (Table 1). The types of maternal thrombophilia abnormalities are listed in Table 3. There was no significant correlation between any lesion and maternal thrombophilia, whether less clinically significant types were included or not. Any combination of two lesions within a placenta was not correlated with maternal thrombophilia. Similarly, the presence of any three, or four or five lesions within a placenta did not correlate with maternal thrombophilia. Extent or severity of septation was not related to maternal thrombophilia.

**Table 1** Relation of placental lesions and maternal thrombophilia in 65 IUFD cases

Septation	Fetal vessel thrombosis	Intimal fibrin cushion	Avascular villi	Haemorrhagic endovasculitis	Fibromuscular sclerosis	MT+	MT–	MTN
13						2	5	6
1	1					0	0	1
1	1	1				1	0	0
2	2	2	2	2		0	1	1
2	2	2	2		2	0	1	1
2	2		2	2	2	0	0	2
1	1				1	0	0	1
1		1				0	0	1
1		1	1		1	0	1	0
3		3			3	0	0	3
1			1			0	1	0
1			1	1		0	1	0
2			2		2	0	0	2
2				2		0	0	2
2				2	2	0	1	1
6					6	0	3	3
	3					1	1	1
	1	1			1	0	0	1
		1				0	1	0
		1	1			1	0	0
			1			0	0	1
				1	1	0	0	1
					5	0	1	4
						1	7	3
41 (63%)	13 (20%)	13 (20%)	13 (20%)	10 (15%)	26 (40%)	6	24	35

IUFD, intrauterine fetal death; MT+, protein S deficiency, factor V Leiden G1691A, prothrombin G20210A gene mutation, lupus anticoagulant, and antiphospholipid syndrome; MT–, compound MTHFR C677T and A1298C heterozygosity, MTHFR 677TT homozygosity, MTHFR C677T or A1298C heterozygosity, and MTHFR 1298CC homozygosity; MTHFR, methyltetrahydrofolate reductase; MTN, normal.

**Table 2** Relation of placental lesions and maternal thrombophilia in 30 livebirth cases

Septation	Fetal vessel thrombosis	Intimal fibrin cushion	Avascular villi	Haemorrhagic endovasculitis	Fibromuscular sclerosis	MT+	MT–
	1					1	0
	1		1			1	0
			1			1	0
		2				1	1
						11	14
0 (0.0%)	2 (6.7%)	2 (6.7%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	19	11

MT+, protein S deficiency, factor V Leiden G1691A, prothrombin G20210A gene mutation, lupus anticoagulant, and antiphospholipid syndrome; MT–, compound MTHFR C677T and A1298C heterozygosity, MTHFR 677TT homozygosity, MTHFR C677T or A1298C heterozygosity, and MTHFR 1298CC homozygosity.

## DISCUSSION

Although the placental lesions that we evaluated would be expected to be manifestations of a fetal thrombotic tendency and have been described under the term fetal thrombotic vasculopathy, that term has been used differently by various investigators. These include placentas with 'multiple (>3) foci of avascular villi',<sup>10</sup> 'obliterated vessels',<sup>11</sup> 'thrombosis of stem villous arteries with downstream avascular villi',<sup>12</sup> 'presence of avascular villi (at least one focus of five or more villi), thrombosis in a vessel of the umbilical cord, chorionic plate or stem villus, haemorrhagic endovasculitis, or intramural deposition of fibrin in a vessel of the umbilical cord, chorionic plate or stem villus',<sup>13</sup> 'any one or more of extensive avascular villi, haemorrhagic endovasculitis, obliterated stem arteries or occlusive thrombi',<sup>14</sup> '15 or more avascular terminal villi per section',<sup>5</sup> 'one or more of segmental areas of avascular villi, occlusive and non-occlusive fetal thrombi, and mural fibrin deposition or calcification within fetal vascular walls'.<sup>15</sup>

The omission of septation of fetal vessels from the definition is puzzling. This may be due to the overwhelming presence of the lesion in stillbirths,<sup>6,16,17</sup> particularly after 48 hours of post-mortem retention.<sup>8</sup> The presence of multiple lumina within the vessel would normally indicate recanalisation of a previously thrombosed vessel;<sup>6,16</sup> thus, it is not surprising that septation of the vascular lumen of fetal vessels has been observed also in placentas of liveborns,<sup>3,6,7,11,16</sup> albeit infrequently, as we confirmed among our liveborn group. Therefore, it was important

that we evaluated this lesion also for any possible correlation with maternal thrombophilia.

Our study has not shown any correlation between maternal thrombophilia and lesions in the placenta that have been described under the umbrella of fetal thrombotic vasculopathy. This is consistent with most studies generally reporting an absence of a relationship between maternal and/or fetal thrombophilia and placental lesions.<sup>18–21</sup> In many of these studies, however, the specific lesion of septation of fetal vessels was not examined.<sup>18</sup> For example, Many *et al.* did not examine any possible association with septation of fetal vessels although they found more infarcts and fibrinoid necrosis of maternal vessels but not more avascular villi in placentas of women with thrombophilia.<sup>10</sup> Maternal thrombophilia was found to be associated with maternal floor infarction, massive perivillous fibrin deposition or fetal vasculopathy; in this study, 9 of 11 placentas with fetal thrombotic vasculopathy had one or more maternal thrombophilias.<sup>12</sup> While septation was not evaluated, maternal factor V Leiden mutation was not associated with fetal thrombotic vasculopathy but fetal factor V Leiden mutation was.<sup>22</sup>

Given that we were evaluating vascular lesions in the fetal side of the placental circulation, a more obvious hypothesis would have been to assess fetal thrombophilia status in relation to these lesions. However, our study was predicated on two practical considerations. Firstly, although possible from the liveborns, we could not test for some fetal thrombophilias such as protein S deficiency or protein C activity from stillbirths. Secondly, and more pertinently, we wanted to know whether the finding of any specific placental lesion should warrant testing for maternal thrombophilia to inform us of the recurrence risk for a subsequent pregnancy. Our finding of an absence of any relationship between those putative histological markers of fetal vascular thrombosis and maternal thrombophilia, extending previous studies which have not examined septation,<sup>18</sup> would suggest not, whether the outcome was a stillbirth or a liveborn infant. It has been suggested that thrombophilia is one of the predisposing factors and umbilical cord lesions may be the second 'trigger' for placental manifestations<sup>23</sup> but we did not find such an association in our cases of stillbirths.

The role of maternal thrombophilia in stillbirths is unclear; no increase in incidence of fetal loss and inherited thrombophilia has been found.<sup>9</sup> While it is probable that further inherited thrombophilia mutations will be described, our finding would support that there is insufficient evidence at present to support routine thrombophilia testing after stillbirths.<sup>19</sup> For the diagnostic anatomical pathologist, the finding of septation in placentas from liveborns is rare and if the lack of a relationship between septation and maternal thrombophilia in

**Table 3** Maternal thrombophilia test results of IUFD cases with and without septation and in livebirth cases

	IUFD		Livebirths
	Septation (n = 41)	No septation (n = 24)	
Clinically significant (MT+)			
Protein S deficiency	0	0	0
Factor V Leiden mutation	0	2	9
Prothrombin gene mutation	1	0	2
Antiphospholipid syndrome	1	0	0
Lupus anticoagulant	1	1	2
Clinically significant (MT–)			
Compound MTHFR heterozygote	5	5	5
Homozygous MTHFR 677TT	3	0	2
Heterozygous MTHFR C677T	2	3	7
Heterozygous MTHFR A1298C	3	1	2
Homozygous MTHFR 1298CC	1	1	1
Total	17	13	30

IUFD, intrauterine fetal death; MTHFR, methyltetrahydrofolate reductase.

stillbirths is extrapolated, then thrombophilia testing is also not recommended.

**Conflicts of interest and sources of funding:** None to declare.

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